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- (b) modifying said protein to neutralize said T-cell epitope  
such that the modified protein induces less than or  
substantially equal the baseline proliferation of T cells in a  
sample.

### REMARKS

#### The Invention.

This invention provides for methods of obtaining proteins which induce a lower allergenic response in humans exposed to the proteins. Specifically, T-cell epitopes of a precursor protein are altered to produce a protein of lowered allergenicity.

#### Status of the Application.

Claims 1-16 are pending with claims 1-12 and 15 and 16 being withdrawn from consideration. The amendment to claim 13 explicitly teaches what was inherent in the definition of T cell neutralization. Support for this amendment can be found on page 11, lines 19 and 20 of the specification.

Claims 13 and 14 stand rejected under 35 U.S.C. § 102 as allegedly anticipated. Claim 13 also stand rejected under 35 U.S.C. § 103(a) as allegedly obvious.

#### Status of the Drawings.

The Applicants acknowledge the filing of informal drawings. Before or concurrent with the payment of an issue Fee, the Applicant will file formal drawings.

#### Sequence Listing.

The Applicants have filed a Sequence Listing concurrently with this Request for Reconsideration.

**35 U.S.C. § 102**

Claim 13 stands rejected under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent 5,593,877 ("the '877 patent). Claims 13 and 14 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent 5,820,862 (the '862 patent).

"A claim is anticipated only if each and every element as set for the in the claim is found, either expressly or inherently described in a single prior art reference."

*Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987).

Claims 13 and 14 call for a modification of a protein so that a T-cell epitope is neutralized, *i.e.*, peptides derived from the modified protein are not identified by a T cell that recognizes peptides derived from the precursor protein and therefore do not bind to the T cell. See, page 5, line 30 of the instant application. However, neither the '877 patent or the '862 patent explicitly or inherently disclose this element of claim 13 and 14. In fact, both of these patents teach the opposite. The peptides of both of these patents are to be used to induce T-cell anergy or non-responsiveness. See column 22, lines 29, *et seq.* of the '877 patent and column 10, lines 58, *et seq.* of the '862 patent

As is well known in the art, ***the induction of T-cell anergy requires binding of peptides*** comprising intact T-cell epitopes to T-cells without the context of MHC class II molecules (see, Janeway, *et al.*, IMMUNOBIOLOGY: THE IMMUNE SYSTEM IN HEALTH AND DISEASE, 4<sup>TH</sup> ED., Garland Publishing, p 279 (1999), enclosed). Without the MHC class II molecules, co-stimulatory factors necessary for a T-cell response are absent and the T-cell becomes anergic and undergoes apoptosis. However, for these events to occur, the T-cell epitope of the native or modified peptide must bind to the T-cell. Thus, T-cell epitopes of the peptides of the '877 and the '862 patent must not be neutralized, *i.e.*, not recognizable by the appropriate T cell.

In contrast, the present invention claims neutralization of a T-cell epitope so that the modified peptide ***does not bind*** a T-cell containing a T cell receptor that binds to the non-modified epitope or protein. See page 5, line 30. Thus, since neither the '877

not a feature of the

not inherent

not a claim element

not a claim element

reference to give by anergy as a loose term

not a claim limitation

patent nor the '862 patent teaches the neutralization of a T-cell epitope of a peptide, neither reference anticipates claims 13 and 14 of the instant invention.

35 U.S.C. §103.

Claim 13, in the alternative, stands rejected as allegedly obvious under 35 U.S.C. § 103(a) over the '877 patent.

In considering obviousness, the prior art as a whole must be considered and its teachings must be viewed as they would have been by one of skill in the art at the time of the invention. To establish a *prima facie* case of obviousness, the Examiner must cite prior art which discloses each element of the claims unless the element would be obvious to one of skill in the art. The Examiner must also provide reasons or motivation for one of skill to carry out the claimed method and demonstrate that one of ordinary skill would have had a reasonable expectation of success in attempting in carrying out the method. *In re Vaeck*, 20 USPQ 2d 1438 (Fed. Cir. 1991).

The Applicants respectfully suggest the Examiner has not made a *prima facie* showing of obviousness in rejecting claim 13. In the first instance, nowhere in the '877 patent does it disclose reducing the allergenicity of a protein by neutralizing the T-cell epitope. Indeed, this reference cannot because the peptides of the '877 patent are used to induce T-cell anergy, which as described above, requires T cell binding. Secondly, there is no motivation, from the '877 patent, to modify the '877 patent to carry out the instant invention. This patent teaches one of skill in the art how to sensitize an allergic individual to a naturally occurring protein. It must teach the induction of anergy because of the impracticality of creating and populating the world with vespids containing modified venom proteins. Because of this inherent limitation of the '877 patent, it cannot provide the motivation to modify the protein so that it doesn't cause an allergic response. Finally, since this reference does not suggest reducing the allergenicity of a protein by neutralizing T-cell epitopes, it cannot possibly provide one of skill with a

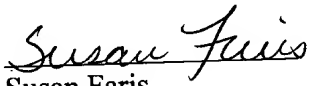
not a  
venom  
anergy

reasonable expectation of success in making proteins less allergenic by neutralizing T-cell epitopes.

In light of the above remarks, the Applicants believe the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-7609.

Respectfully submitted,

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## Appendix I

13. (Once amended) A method of reducing the allergenicity of a protein comprising the steps of:
- (a) identifying a T-cell epitope in said protein;
  - (b) modifying said protein to neutralize said T-cell epitope such that the modified protein induces less than or substantially equal the baseline proliferation of T cells in a sample.
14. The method according to claim 13, wherein said epitope is modified by:
- (a) substituting the amino acid sequence of the epitope with an analogous sequence from a human homolog to the protein of interest;
  - (b) substituting the amino acid sequence of the epitope with an analogous sequence from a non-human homolog to the protein of interest, which analogous sequence produces a lesser allergenic response from T-cells than that of the protein of interest; or
  - (c) substituting the amino acid sequence of the epitope with a sequence which substantially mimics the major tertiary structure attributes of the epitope, but which produces a lesser allergenic response from T cells than that of the protein of interest.